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To cite this article: A.V. Myshkina *et al* 2020 *J. Phys.: Conf. Ser.* **1461** 012111

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Gd₂O₃, SiO₂-Gd₂O₃ and SiO₂-MnO₂ nanoparticles as potential MRI contrast agents

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Abstract. Gd₂O₃, SiO₂-Gd₂O₃ and SiO₂-MnO₂ nanoparticles were produced by the method of pulsed electron evaporation of oxide targets with condensation of the vapors in a vacuum. These materials are considered as probable contrast agents for magnetic resonance imaging (MRI). The Gd₂O₃ nanoparticles exhibit a rather high r1 and r2 relaxivities. These results point to the potential of using nanocrystals for MRI diagnosis. The mesoporous nanostructures SiO₂-Gd₂O₃ and SiO₂-MnO₂ could be considered as multimodal theranostic agents.

1. Introduction

In recent years magnetic resonance imaging (MRI) has become one of the leading research methods and its diagnostic capabilities continue to expand. The use of contrasting agents plays a significant role in this process and allows the differential diagnosis of pathological neoplasms with a complex structure (for example, small-sized tumors and / or metastatic lesions).

Currently, a search for new contrast agents is intensively conducted [1-5]. Many of these materials are classified as nanoparticles. On the one hand, interest in the use of nanoparticles in MRI imaging is caused by the high sorption capacity of materials due to the developed surface, so that nanoparticles can approach biological objects, interact and connect with them. On the other hand, the magnetic properties of the substance change significantly during the transition to the nanostructure, as a result of which nanomaterials get unusual ferro- and superparamagnetic properties.

Currently, gadolinium-based compounds using organic chelates are widely used for MRI contrast [6]. This is due to the fact that the gadolinium ion Gd(III) has seven unpaired f-electrons and a symmetric S-state, which determines the large magnetic moment on the one hand, and the slow relaxation of the nuclear magnetization, which is necessary in terms of the efficiency of the paramagnetic contrast agent on the other hand. However, due to the known toxicity of gadolinium ions Gd(III), the search for new biocompatible contrast agents, including those based on metal oxide nanoparticles, is actively conducted [2]. Such agents include gadolinium oxide Gd₂O₃ nanoparticles of small sizes [7]. Experimental studies have shown that these nanoparticles exhibit high values of relaxivity.

Another promising agent for use as a contrast agent in MRI is manganese oxide [8]. In recent years, there are works devoted to the study of the properties of nanoparticles of various manganese oxides. It



has been shown that the main parameters of contrast agents from manganese oxides are not inferior to those of contrast agents based on gadolinium oxides [9, 10]. In addition, manganese ions are involved in biochemical processes, which allow to consider them as biocompatible materials.

In order to reduce aggregation in aqueous suspensions, decrease toxicity, enhance contrast properties and targeted delivery of nanoparticles, nanoparticles coated with various shells (organic acids, dextran, silicon dioxide, etc.) are actively studied [11]. The use of silicon oxide in the composition of nanocomplexes is particularly interesting in terms of the ability to create porous structures on its basis for further implementation of targeted delivery [12].

The purpose of this work is to study the relaxation of gadolinium oxide Gd_2O_3 nanoparticles, mesoporous nanostructures $SiO_2-Gd_2O_3$ and SiO_2-MnO_2 synthesized by gas-phase evaporation of ceramic targets by electron beam, as well as to assess the possibility of their use as MRI contrast agents.

2. Experimental

We have used a NANOBIM-2 unit (Institute of Electrophysics, Ural Branch of the Russian Academy of Science) to produce Gd_2O_3 , $SiO_2-Gd_2O_3$ (10% of Gd_2O_3) and SiO_2-MnO_2 (10% of MnO_2) nanoparticles. The unit realizes the method of pulsed electron evaporation of ceramic oxide targets with condensation of the vapors in a vacuum or low-pressure gas and allows us to obtain nanopowders of oxides with a high specific surface area up to 330 m²/g with an average size of 3-10 nm [13]. The details of nanomaterial synthesis correspond to papers [14-16].

The nanoparticles were dispersed in distilled water in the concentration range 50-500 µg/ml. The choice of agent concentrations is determined by the compliance with the dosages used in clinical animal studies [4, 5]. The sodium citrate and polyethylene glycol were used as suspension stabilizers. The dispersion was thoroughly mixed and treated with ultrasound for 40 min. The stability of the aqueous nanoparticles suspensions was assessed using a sedimentation analysis consisting in measuring the time dependence of the transmittance of the aqueous suspension using a PE-5400 VI spectrophotometer.

Relaxation characteristics were measured using a NMR relaxometer (M.N. Mikheev Institute of Metal Physics, Ural Branch of the Russian Academy of Science). The magnitude of the magnetic field was 0,18 T, operating frequency – 4,3 MHz. The saturation recovery (SR) pulse sequence was used to measure the spin-lattice relaxation time T₁, the pulse sequence Carr-Purcell-Meiboom-Gill (CPMG) was used to measure the spin-spin relaxation time T₂.

3. Results and discussion

3.1. A stability of aqueous nanoparticle suspensions

The stability of aqueous suspensions of gadolinium oxide Gd_2O_3 with stabilizers PEG 2000 in ratio of 1:1, and sodium citrate ($Na_3C_6H_5O_7$) in ratios of 1:1 and 2:1 (nanoparticle : stabilizer) was studied. Gadolinium oxide nanoparticles Gd_2O_3 with PEG 2000 stabilizer rather quickly settle in a solution, which is probably due to the process of adhesion of fine particles of dispersed systems in larger under the influence of adhesion forces with the formation of coagulation structures (effect of coagulation). Water suspensions Gd_2O_3 with sodium citrate in ratio 2:1 showed the best stability. In this case the rate of colloid sedimentation was about 1% per hour.

Mesoporous $SiO_2-Gd_2O_3$ and SiO_2-MnO_2 nanostructures showed better stability in aqueous solutions compared to pure Gd_2O_3 nanoparticles. Probably, the presence of silicon oxide in the composition of the nanocomplex prevents the processes of adhesion of nanoparticles and their aggregation in aqueous solutions. Adding sodium citrate stabilizer to aqueous solutions $SiO_2-Gd_2O_3$ and SiO_2-MnO_2 decrease the rate of colloid sedimentation up to 1% per hour.

3.2. Relaxivities of nanoparticle suspensions

The investigated Gd_2O_3 , $SiO_2-Gd_2O_3$ and SiO_2-MnO_2 nanoparticles belong to paramagnetic particles. When assessing the possibility of using these compounds as contrasting agents, they should be

considered primarily as positive agents (affecting the intensity of the MR signal by reducing the time of spin-lattice relaxation T1). Such compounds create local magnetic field gradients that violate the homogeneity of the magnetic field in these places.

For the sample groups studied, the times of spin-lattice relaxation T1 and spin-spin relaxation T2 were determined, the relaxation rate (r_1 and r_2 , units – $\text{mM}^{-1}\text{s}^{-1}$) was estimated. Relaxivity can be calculated by the following formula [17]: $R_i = 1/(C[\text{mM}] \cdot T_i[\text{s}])$, where C is the concentration of nanoparticles, mM; T_i (T1 or T2) is the measured time of spin-lattice or spin-spin relaxation, s.

Figures 1-2 show the graphs of the inverse value to the relaxation times, depending on the concentration of solutions in units of mM. The tangent of the slope angle of the line, which is the result of the linear approximation of the experimental curve, is the desired value of the relaxation rate. The results of r_1 and r_2 relaxivities estimation are shown in Table 1.

As shown in Fig.1 the relaxivity of pure gadolinium oxide nanoparticles Gd_2O_3 suspensions is sufficiently high, which corresponds to the literature data [7, 18]. The relaxivities of $\text{SiO}_2\text{-Gd}_2\text{O}_3$ and $\text{SiO}_2\text{-MnO}_2$ nanostructures are almost two orders of magnitude lower due to the relatively low (10%) concentration of paramagnetic particles in the complex. It should also be noted that the ratio of relaxation parameters r_2/r_1 is about 1, which is typical for dual contrast agents in MRI.

Table 1. Relaxivities r_1 and r_2 for Gd_2O_3 , $\text{SiO}_2\text{-Gd}_2\text{O}_3$ and $\text{SiO}_2\text{-MnO}_2$ nanoparticles.

Nanoparticle	r_1	r_2
Gd_2O_3	2,03	2,18
$\text{SiO}_2\text{-Gd}_2\text{O}_3$ (10% of Gd_2O_3)	0,05	0,07
$\text{SiO}_2\text{-MnO}_2$ (10% of MnO_2)	0,04	0,06

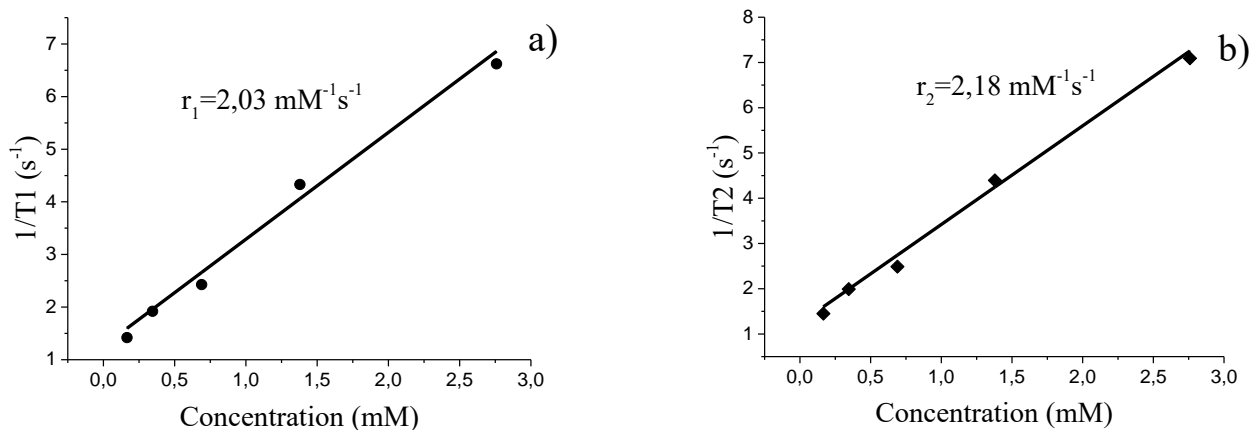


Figure 1. Relaxivities r_1 (a) and r_2 (b) of Gd_2O_3 nanoparticle suspensions

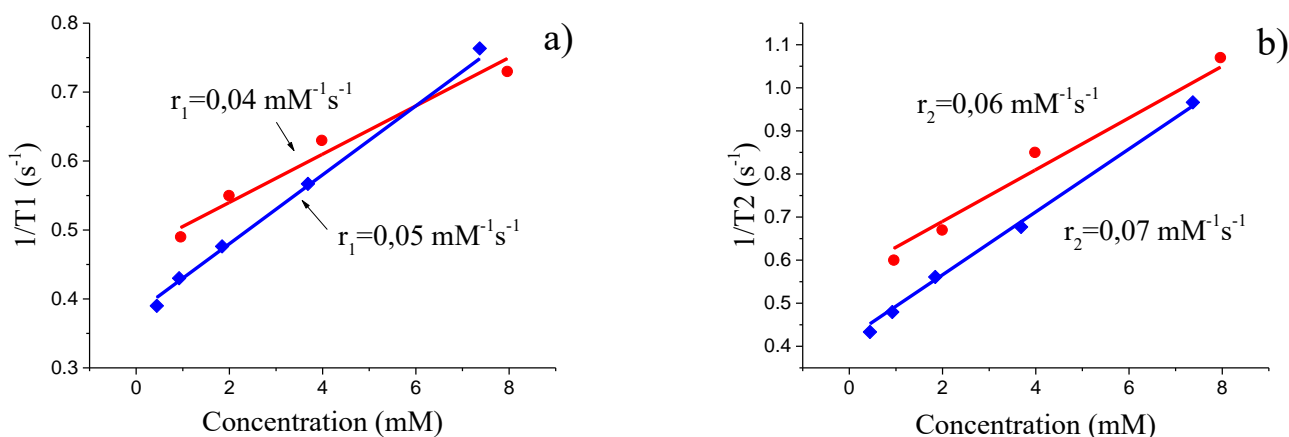


Figure 2. Relaxivities r_1 (a) and r_2 (b) of SiO₂-Gd₂O₃ (blue curve) and SiO₂-MnO₂ (red curve) nanoparticles

4. Conclusion

The possibility of using gadolinium oxide Gd₂O₃ nanoparticles, as well as SiO₂-Gd₂O₃ and SiO₂-MnO₂ nanostructures for contrast in magnetic resonance imaging has been studied. The stability of aqueous nanoparticle suspensions was estimated and it was shown that the optimal conditions are realized when using sodium citrate stabilizer in ratio of 2:1 (nanoparticle : stabilizer).

The relaxation characteristics of several groups of samples with various concentrations were measured. Relaxation parameters for the studied groups are calculated. We could conclude that the relaxivities r_1 and r_2 suspensions based on gadolinium oxide Gd₂O₃ nanoparticles are comparable with the values for the studied «analogues». The relaxivity parameters for SiO₂-Gd₂O₃ and SiO₂-MnO₂ nanoparticles are much smaller, but they have a porous structure, which allows them to be considered as multimodal agents for diagnostics and targeted delivery. It should be noted that the ratio of relaxation parameters r_2/r_1 for all the samples studied is close to 1, which allows them to be used for contrasting T1 - and T2-weighted images.

References

- [1] Xiao Y, Paudel R, Liu J et al 2016 *International Journal of Molecular Medicine* **38** 1319-1326.
- [2] Xu W, Kattel K, Park J Y et al 2012 *Physical Chemistry Chemical Physics* **14** (37) 12687-700.
- [3] Sosnovik D E, Nahrendorf M, Weissleder R 2008 *Basic Res Cardiol* **103** (2) 122-130.
- [4] Sjögren C E, Johansson C, Naevestad A et al 1997 *Magn Reson Imaging* **15** 55-67.
- [5] Bulte J W, Kraitchman D L 2004 *HMR Biomed* **17** 484-499.
- [6] Rogosnitzky M, Branch S 2016 *BioMetals* **29** (3) 365-376.
- [7] Kim T J, Chae K S, Chang Y, Lee G H et al 2013 *Curr. Topics in Med. Chem.* **13** (4) 422-433.
- [8] Pan D, Schmieder A H, Wickline S A, Lanza G M 2011 *Tetrahedron* **67** 8431-8444.
- [9] Kim T, Momin E, Choi J et al 2011 *Journal of the American Chemical Society* **133** 2955-2961.
- [10] Xiao J, Tian X M, Yang C et al 2013 *Scientific Reports* **3** 3424.
- [11] Lee J E, Lee N, Kim T et al 2011 *Accounts Of Chemical Research* **44** (10) 893-902.
- [12] Ksenofontova O I, Vasin A V, Yegorov V V 2014 *Technical Physics Journal* **84** (1) 67-78.
- [13] Sokovnin S Y, Ilves V G, Zuev M G 2016 *Engineering of Nanobiomaterials* **2** 29-75.
- [14] Il'ves V G, Sokovnin S Y, Uporov S A, Zuev M G 2013 *Phys. of the Sol. St.* **55** (6) 1262-1271.
- [15] Ilves V G, Murzakaev A M, Sokovnin S Y 2018 *Microp. and Mesop. Materials* **271** 203-218.
- [16] Zlygosteva O A, Sokovnin S Y, Ilves V G 2018 *Physical and Chemical Aspects of Studying Clusters, Nanostructures and Nanomaterials* **10** 262-269.
- [17] Rink P A Magnetic resonance in medicine 1995 Oxford, Backwell scientific publications.
- [18] Gu W, Song G, Li S et al 2014 *RSC Adv.* **4** 50254-50260.